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ANTIPHOSPHOLIPID SYNDROME (S ZUILY, SECTION EDITOR)

Obstetric Anti-phospholipid Syndrome: State of the Art

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Abstract

Purpose of Review This review focuses on new pathogenesis and clinical-therapeutic aspects of obstetric anti-phospholipid syndrome (ob-APS) in the last 5 years.

Recent Findings The pathogenesis of ob-APS is multifactorial, including placental infarctions, infiltration of inflammatory cells that cause acute and chronic inflammation, leading to uncontrolled inflammation and poor pregnancy outcomes. A preconception counseling and a patient-tailored treatment are fundamental to improve maternal and fetal outcomes. Thanks to conventional treatment, based on low-dose aspirin and heparin, 70% of women with ob-APS can have successful pregnancies. Women with positive anti-phospholipid antibodies (aPL) without clinical manifestations ("aPL carriers") or with obstetric manifestation not fulfilling ob-APS criteria need to be further investigated in order to assess their best management.

Summary Great interest has been given to drugs that could interact in the pathophysiological mechanisms, such as hydroxychloroquine, statins, and eculizumab. These drugs could be considered for patients refractory to conventional therapy.

Keywords Anti-phospholipid syndrome · Anti-phospholipid antibodies · Pregnancy morbidity · Obstetric complications · Pathogenesis · Management · Treatment

Introduction

Anti-phospholipid syndrome (APS) is a systemic autoimmune disease characterized by arterial and/or venous thrombosis and/or obstetric morbidity mediated by anti-phospholipid antibodies (aPL). These pathogenic autoantibodies are determined by means of lupus anticoagulant (LA), IgM and IgG anti-cardiolipin (aCL), and anti-β2glycoprotein-I (aβ2GPI) antibodies; their presence should be confirmed in two different occasions at least 12 weeks apart [1].

Even though the syndrome was initially described as a single disorder, the distinction between obstetric (ob-APS) and thrombotic APS has been well established during the last 10 years given the following observations: (1) patients can display vascular thrombosis with no pregnancy complications or, alternatively, obstetric manifestations alone [2]; (2) the coexistence of both thrombosis and miscarriages only affects about 2.5–5% of APS pregnancies [3]; (3) IgG fractions from pure ob-APS display different effects in vitro on monocyte and trophoblast cells [4].

The ob-APS can affect both the mother and the fetus [5]. The clinical criteria of ob-APS were revised in 2006, as follows: history of three early consecutive miscarriages (< 10 weeks of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded), and/or one stillbirth (> 10 weeks of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus), and/or one intra-uterine growth restriction (IUGR) or a premature birth before 34 weeks of gestation due to pre-eclampsia (PE) or eclampsia or placental insufficiency (abnormal or non-reassuring fetal surveillance test, abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, oligohydramnios, and postnatal birth weight less than the 10th percentile for the gestational age) [1]. Furthermore, pregnant women with ob-APS have an increased risk of thrombosis [5],

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thrombocytopenia, and HELLP syndrome (hemolytic anemia, elevated liver enzymes, and low platelet count) [6].

This narrative review summarizes the latest research on pathological, clinical, and therapeutically aspects of ob-APS.

Epidemiology

APS can occur as an isolated disease (primary) or associated with other systemic autoimmune diseases (secondary), mainly with systemic lupus erythematosus (SLE). Robust epidemiological data from large controlled population studies are still lacking. Women are more commonly affected by APS than men, in primary (3.5:1 ratio) as well as in secondary APS (7:1) [7].

According to the review of the literature, aPL are positive in approximately 6% of women with pregnancy morbidities (pregnancy losses, IUGR, PE/eclampsia, and HELLP syndrome) [8].

Pathogenesis

The exact mechanisms involved in the prothrombotic state of the disease (causing thrombosis and/or obstetric complications) remain yet to be fully explained. aPL have the ability to induce thrombus formation in the arterial and/or venous vasculature and/or microcirculation by targeting and affecting the functionality of a variety of cell types such as endothelial cells, monocytes, leukocytes, neutrophils, and platelets on the vascular aspect of the disease, and trophoblasts and decidual cells during gestation; the irregular function of these cells contributes in the disease development [9]. Several studies have reported that aPLs have the capacity to interact with the trophoblast and the endothelial cell monolayer, by disrupting the anticoagulant annexin A5 shield, resulting in fetal loss [10].

However, De Wolf et al. and Stone et al., in histopathologic findings in the human placenta samples, have demonstrated that other non-thrombotic mechanisms, such as inflammation, may be involved in the pathogenesis of ob-APS, besides placental infarctions [11, 12] (Table 1). Viall et al., in a recent meta-analysis of the histopathologic findings in the placentae from aPL-affected pregnancies, revealed five features associated with aPL: (1) placental infarction, (2) impaired spiral artery remodeling, (3) decidual inflammation, (4) increased syncytial knots, and (5) decreased vasculosyncytial membranes [36].

Table 1 Pathogenic mechanisms of ob-APS

	Pathogenic mechanism	References
Thrombosis	In vitro models:	[13]
	• aPL interact with endothelial cells, predominately by binding to β_2GPI expressed on the cell membranes of different cell types, and induces a procoagulant and pro-inflammatory endothelial state	
	• aPL upregulate TF expression on endothelial cells and blood monocytes, as well as, by promoting endothelial leukocyte adhesion, cytokine secretion and PGE2 synthesis	[14–17]
	• aPL recognize phospholipid-binding proteins expressed on platelets and induces platelet aggregation induced by another agonist	[18, 19]
	• aPL interferes with plasma components of the coagulation cascade by inhibiting anticoagulant activity, reducing fibrinolysis, and disrupting annexin A5 shield of the trophoblast and endothelial cell monolayers	[13, 18, 20, 21]
	In vivo models:	
	• infusion of aPL with or without β2GPI alters expression of endothelial adhesion molecules, causing upregulation of NO and TF expression causes vascular abnormalities (especially in the arterial endothelium)	
	• Thrombotic effects were produced using affinity-purified anti-β_2GPI IgG, and were inhibited by specific absorption of anti-β_2GPI activity	[22, 23]
Inflammation	In vitro models:	[24]
	• aPL, via TLR-4 and MyD88, induce trophoblasts to secrete IL-1β and IL-8	
	• Downstream of MyD88, IL-1β secretion is mediated by uric acid, which in turn activates NLRP3 inflammasome to process IL-1β	[25]
	• Trophoblast inflammation is driven by aPL induced miR-146a-3p and uric acid which activate TLR-8 and the NLRP3 inflammasome in trophoblasts	[26]
	• Decidual stromal cells treated with a β2GPI-dependent aPL monoclonal antibody, express an upregulation of genes involved in the inflammatory response	[27, 28]
	In vivo models:	[29–31]
	• aPL located in the placenta and inflammation (by complement activation and recruitment and stimulation of neutrophils is the main factor in placental insufficiency, fetal loss, and IUGR)	
	• C5 is the key effector and acts through the upregulated expression of TF on neutrophils infiltrating placental tissues	
Complement activation	In vivo models:	[22, 32–34]
	• Animals deficient in complement components or complement receptors, or treated with complement inhibitors were protected from thrombogenic effect of aPL	
	• Complement deposition was found in placenta tissue from women positive for aPL, in retrospective study	[35]

aPL anti-phospholipid antibodies, *LAA* low avidity autoantibodies, *β_2GPI* β_2 glicoprotein I, *NO* nitric oxide, *TF* tissue factor, *IL* interleukin, *TLR* toll-like receptor, *MyD88* myeloid differentiation factor 88, *miR* microRNA

aPL recognizing β2GPI have been shown to be pathogenic in ob-APS due to its constant expression on the cell surface [10]. The placenta is a major target for β2GPI-dependent pathogenic aPL binding and consequently reducing trophoblast differentiation/invasiveness [10]. This was demonstrated by 14 studies that investigated trophoblast invasion in the presence of aPL in vitro. Both the outer placental syncytiotrophoblast (STB) and the extravillous trophoblast (EVT) bind to aβ2GPI antibodies differently; the STB internalized aPL via a low-density lipoprotein receptor (LDLR), and the EVT maintains aPL on the cell surface [37••, 38].

During the first trimester, if maternal spiral arteries are not sufficiently plugged by endovascular trophoblasts, then strong stream of blood from the arteries may physically or oxidatively damage the placenta and contribute to early pregnancy loss [39]. As gestation progresses, if trophoblasts do not transform the maternal spiral arteries into wide-bore tubes adapted for efficient blood flow, the placenta may become hypoperfused and undergo ischemia-reperfusion injury, leading to PE and IUGR [40].

In vitro studies, using human first-trimester EVT, demonstrated that aPL recognizing β2GPI trigger EVT to produce elevated levels of pro-inflammatory cytokines and chemokines, inhibit spontaneous trophoblast migration, increase trophoblast antiangiogenic soluble endoglin secretion, and disrupt trophoblast-endothelial interactions in a model of spiral artery transformation, reproducing similar changes to those in PE [41, 42].

Two in vitro studies demonstrated that aPL induce trophoblasts inflammation by secreting interleukin-1β (IL-1β) and IL-8 via activation of Toll-like receptor 4 (TLR-4) and its adapter protein myeloid differentiation factor 88 (My88) [24, 25]. Downstream of My88 and IL-1β is mediated by uric acid which activates NLRP3 inflammasome to process IL-1β and IL-8 production; downstream of TLR-4 is mediated by induction of microRNA-146a-3p (miR 146a-3p). aPL-induced miR-146a-3p and uric acid act as endogenous secondary signals for activation of TLR-8 and NLRP3 inflammasome in trophoblasts, to drive trophoblast inflammation [43]. A recent in vitro study demonstrated that aβ2GPI aPL induce altered TAM receptor signaling (negative regulator of TLR) and autophagy causing, respectively, subsequent TLR4-mediated IL-8 response and NLRP3 inflammasome-mediated IL-1 activity leading to a robust inflammatory response [44•].

Reduced trophoblast migration and invasion caused by aPL are mediated by apolipoprotein E receptor 2 (ApoER2) which interacts with dimerized β2GPI. ApoER2 serves as a target for anti-β2GPI-β2GPI complexes leading to reduced pro-migratory IL-6 and STAT-3 activity. In vivo studies have demonstrated the role of ApoER2 in aPL-mediated feta loss and IUGR [27].

However, there seems to be a difference between the pathogenesis of aPL-related recurrent pre-embryonic loss and late pregnancy morbidity. Especially for early pregnancy losses, the effects of aPL on placentation may be relevant, as these autoantibodies increase apoptosis and reduce invasion of the trophoblast [45]. The complement system, instead, seems to play a crucial role in causing pregnancy loss and fetal growth restriction. Shamonki et al, in human studies, showed that placenta of women with aPL has increased complement deposition of C4d and C3b, supporting the hypothesis that complement activation is involved in the pathogenesis of aPL-related pregnancy complications [35, 36]. Inherited hypofunctional variants of complement regulators provide an increased risk of PE in women with SLE and/or aPL [46]. A recent study in pregnant patients with SLE and/or aPL, increased levels of Bb and sC5b-9, complement activation products, early in pregnancy were significantly associated with adverse pregnancy outcomes (APOs) [47•].

A mediator that plays an important role in the complement activation is the tumor necrosis factor (TNF). This mediator links complement C5a-C5aR interactions and pathogenic aPL to fetal damage [48]. aPL that target decidual tissue cause a rapid increase in decidual and systemic TNF levels. Studies on mice have suggested that miscarriages induced by aPL are less frequent in those who are deficient in TNF or treated with TNF blockade. In humans, TNF contributes to the pathogenesis of poor pregnancy outcomes: TNF-α increases throughout pregnancy and has been related to miscarriages, fetal losses, PE, and preterm birth as well as IL-10 reduction [49].

As described above, placental infarction due to thrombus occluding spiral artery is a common histopathologic finding in ob-APS. In two studies that examined the placentae from first trimester abortions, placental thrombotic infarction or spiral artery thrombosis were not detected, this suggests that this phenomenon could be associated with late pregnancy complications [50, 51].

Another factor that also plays an important role in the pathogenesis of PE in SLE patients is Interferon (IFN)α. In vitro and in vivo studies suggest that elevated IFN-α levels contribute in developing PE by sensitizing maternal endothelium to the antiangiogenic effects of soluble Flt-1 and by inhibiting transcription of proangiogenic VEGF, necessary for homeostasis in some vascular beds. Increased IFN-α levels may identify SLE patients who have an increased risk of developing placenta-mediated pregnancy complications; this may be related to the vasculopathic effects of elevated IFNα in active SLE patients who experience PE early in pregnancy [52].

Predictive Factors of Obstetrical Outcome

Risk factors associated with adverse pregnancy outcomes include: high number of previous pregnancy losses [53], thrombotic APS [54, 55], associated autoimmune diseases (SLE)

[56], hypocomplementemia at conception [57, 58, 59•], high antibody titer [60, 61], and the number and the type (LAC and IgG aCL) of different autoantibodies detected, with an increased risk in patients with a triple-positive profile [55, 61, 62]. The presence of triple aPL positivity seems to be due to antibodies directed to the first domain of β2GPI, anti-D1 [63, 64]. These pathogenic antibodies are more frequent in patients having higher antibody titers and triple positivity for aPL. This seems to make sense because these pathogenic antibodies have LA activity [65]. On the other hand, single positivity for the aPL profile seems to be associated with positive tests for anti-domain 4/5, considering these are non-pathogenic antibodies [66]. Interestingly, it has been recently demonstrated that anti-D1 are significantly associated with pregnancy morbidity, in particular late pregnancy morbidity (late pregnancy losses and premature delivery) [67•]. Data from the study PROMISSE showed that LA was the only aPL associated with APOs after the first trimester [68].

As for the antibody titer, conflicting results exist. Even though high positive antibody titers are associated with adverse pregnancy outcome [60, 61], there is increasing evidence that patients with low-titer aPL can experience poor pregnancy outcomes similarly to high-titer aPL patients [69–73]. These observations suggest that in contrast to thrombotic events, low-titer aPL can play a significant role in ob-APS and that the current classification criteria may not allow to include all the ob-APS cases.

Future prospective studies with homogeneous study population and design are needed to clarify these findings and to identify additional risk factors and better delineate the optimal personalized risk-based management of these women.

Clinical Manifestations

The frequency of obstetric complications varies among studies and depends on the selected APS phenotype and on the treatment regimen [74]. The rates of PE range from 2 to 17%, venous thrombosis 2–3%, IUGR 3–12%, preterm delivery 11–19%, hypotrophy 11–23%, and neonatal complications 11–13% [75, 76]. In the PROMISSE study, Lockshin et al. reported an overall APO of 19% after exclusion of early pregnancy loss [76].

In a multicenter prospective study, the Euro-Phospholipid project, 1000 APS European patients were followed during a 10-year period [77••]. A total of 188 pregnancies occurred in 127 women and 72.9% ($n = 137$) of pregnancies succeeded in having one or more live births. The most common obstetric complication was early pregnancy loss (< 10 weeks) in 16.5% ($n = 31$) of pregnancies. The obstetric morbidity rate was lower during the last 5 years of the study; no women developed PE/eclampsia. Regarding fetal morbidity, the most frequent manifestations were birth prematurity (48.2% of the total live birth) and IUGR (26.3%) [77••]. In a European cohort of 247 ob-APS (EUROAPS), live births were achieved in 192/247 cases (77.7%). Of these 192 successful cases, 174 (89.7%) received treatment and 18 (10.3%) did not. Obstetric complications appeared in 129/247 (52.2%) cases, although not all ended in fetal demise or stillbirth. Fetal loss was the most frequent fatal complication (17.80%) followed by miscarriage (16.27%), with stillbirth being relatively infrequent (4.69%). Prematurity was the most common non-fatal complication (47.28%). Early and severe PE together with HELLP syndrome appeared in more than 18% of these women. IUGR complicated 15.50% of cases [78]. Patients with ob-APS mainly suffer from obstetrical morbidity, but the risk of thrombotic events persists during the follow-up [5, 78, 79].

Management of ob-APS

General Considerations

The management of women with ob-APS includes a close surveillance and tailored treatment before, during, and after pregnancy to optimize maternal and fetal pregnancy outcomes.

As stated in the EULAR recommendations [80••], a preconception counseling is fundamental to assess any previous pregnancy complications and/or thrombotic events, the presence of the "APS non-criteria manifestations" [80••], other associated autoimmune diseases (SLE), genetic thrombotic risk factors, major organ involvement, the presence of other comorbidities, life style risk factors (e.g., smoking, alcohol consumption), medications that may compromise fetal development, and the risk stratification according the aPL profile (Table 2).

Thanks to counseling and risk stratification assessment, it is possible to set up preventive strategies and a patient-tailored monitoring plan. If possible, visits and blood tests should be performed monthly, although a less tight schedule can be planned for low-risk patients. In addition to the routine first and second ultrasonography screening, patients with ob-APS should undergo supplementary surveillance in the third trimester, at monthly intervals, based on biometric and Doppler findings, in order to diagnose an early or late IUGR and plan the time of delivery [80••]. In patients with current or past renal involvement, blood pressure and 24-h urine proteinuria should be regularly monitored.

Obstetric APS

Current standard of care for women with ob-APS includes *prophylactic* or *therapeutic* dose of heparin (unfractionated heparin-UFH- or low-molecular weight heparin-LMWH) combined with low dose of aspirin (LDA) (75–100 mg/day)

Table 2 Suggested management of obstetric-APS

		Management
General measures		Folic acid preferably for at least 3 months prior to conception and throughout pregnancy Calcium and vitamin D during pregnancy During puerperium, prevent immobility and use compression stockings if history of thrombosis
"Criteria" ob-APS	Pregnancy	Conventional treatment: LDA[a)□] (75–100 mg/day) plus prophylactic LMWH[□] or UFH[□]
Refractory ob-APS (with previous pregnancy failure on conventional treatment)		LDA[a)□] (75–100 mg/day) plus prophylactic/therapeutic LMWH[□] or UFH[□] and consider one or more of the following additional treatments: - Prednisolone (10 mg/day) in the first trimester (0–14 weeks of gestation) - IVIG (400 mg/kg/day for 5 consecutive days or 1 g/kg daily for 2 consecutive days - Plasmapheresis (3 to 5 consecutive days) - HCQ (5–6 mg/kg/day) - Pravastatin (20 mg/day)
	Puerperium	Prophylactic LMWH[□] or UFH[□] for 4–6 weeks
APS patients with previous thrombosis	Pregnancy	Stop VKA[□] (before the sixth week of gestation)** start LDA[a)□] (75–100 mg/day) plus therapeutic UFH[□] or LMWH[□]
	Puerperium	Therapeutic UFH or LMWH OR VKA**
CAPS, during pregnancy		First-line therapy UFH*[□] (80 U/kg IV bolus) then continuous infusion of 18 U/kg/h Glucocorticoids methylprednisolone (IV) 500–1000 mg/day for 1 to 3 days and slowly reduce to 1–0.5 mg/kg/day (depending on clinical condition) Plasmapheresis (three to 5 consecutive days) and/or IVIG (2 schemes, after plasmapheresis) 400 mg/kg/day for 5 consecutive days or 1 g/kg/month Second-line therapy RTX [375 mg/m^2 (IV) 1/week during 1 month or 1 g twice 15 days apart] or Eculizumab [900 mg (IV)/week for 4 weeks then 1200 mg/2 weeks]
APS associated to autoimmune diseases (e.g., SLE)	Pregnancy	LDA[a)□] (75–100 mg/day) plus prophylactic/therapeutic LMWH[□] or UFH[□] (prophylactic/therapeutic weight-adjusted dose depending the main clinical manifestation of APS, thrombotic or obstetric) and HCQ (5–6 mg/kg/day)
	Puerperium	Prophylactic UFH or LMWH for 4–6 weeks
aPL carriers or women not fulfilling clinical criteria for ob-APS •"Low-risk"[#] aPL profile •"High-risk"[#] aPL profile and/or additional risk factors and/or APS non-criteria manifestations	Pregnancy	LDA[a)□] (75–100 mg/day) LDA[a)□] (75–100 mg/day) plus UFH[□] or LMWH[□] (prophylactic weight-adjusted dose depending on aPL profile plus concomitant risk factors and/or additional APS non-criteria manifestations) According to individual risk stratification, consider adding HCQ 5–6 kg/day
	Puerperium	Prophylactic UFH[□] or LMWH[□] for 4–6 weeks

aPL anti-phospholipid antibodies, *APS* anti-phospholipid syndrome, *CAPS* catastrophic anti-phospholipid syndrome, *IV* intravenous, *IVIG* intravenous immunoglobulins, *ob-APS* obstetric-anti-phospholipid syndrome, *RTX* rituximab, *UFH* unfractionated heparin, *U* units, *LMWH* low molecular weight heparin, *kg* kilogram, *hr* hour, *mg* milligram

[#] "low-risk" profile (patients with isolated, intermittently positive aCL, or aβ2GPI at low-medium titers); "high-risk" aPL profile: LA positivity, or "triple positivity"—LA + aCL + aβ2GPI—or medium-high titers of IgG aCL or IgG aβ2GPI

* Acute phase

** Warfarin: teratogenic, especially between the 6th and 10th week of gestation; risk of fetal bleeding specially after the 32th week of gestation. During puerperium, it can be restarted after bridging therapy with heparin

[a)] Depending on formulations of the drug available in different countries

LDA should be started prior to conception and stopped before delivery depending on the local protocol. Heparin should be started when pregnancy is confirmed (at positive pregnancy test or after ultrasound confirmation, depending on local protocols) and stopped before delivery depending on the type of heparin and the mode of delivery

[□] In pregnant women with APS and thrombocytopenia, a frequent APS non-criteria manifestation, the use of heparin, LDA, and VKA should be carefully evaluated due to the increased risk of bleeding. If thrombocytopenia is mild, above 50×10^9/L, and no signs of bleeding, anti-thrombotic treatment can be continued. If platelet count is below 50×10^9/L, the use of anti-thrombotic drugs should be weighed against the risk of clotting

[80••, 81]. The LDA should be preferably given prior to conception, and LMWH or UFH treatment should begin as soon as pregnancy is confirmed. It has been demonstrated that both UFH plus LDA and LMWH plus LDA are effective in the management of recurrent abortion secondary to APS [82–84]. Given the similar efficacy with both types of heparin, LMWH could be preferred for practical reasons due to its route of administration and no need for monitoring and for its lower risk of osteoporosis [85]. Regarding the dosage of *prophylactic* heparin, it is unknown if fixed doses are equal or more efficacious than adjusted ones in preventing APOs. Just one prospective study showed that weight-adjusted, once daily, doses of LMWH combined with LDA could be an efficacious treatment option for pregnant APS patients with no history of thrombosis [56]. However, in clinical practice, most physicians use a fixed dosage of LMWH in pregnant APS.

In ob-APS patients with higher risk to develop a first thrombotic event, due to the "high-risk" aPL profile and concomitant risk factors and/or additional "APS non-criteria manifestations," *therapeutic* dose of heparin should be preferred [80••].

Refractory Obstetric APS

However, current management does not prevent all maternal, fetal, and neonatal complications of APS, and the current treatment fails in 20 to 30% of APS pregnancies, raising the need to explore other treatments to improve obstetrical outcome. In these women with refractory ob-APS, treatment options to improve pregnancy outcomes include prednisolone (10 mg/day, 0–14 weeks) and/or intravenous immunoglobulin (IVIG) and/or plasmapheresis [86, 87•]. Great interest has been given to drugs that could interact in the pathophysiological mechanisms of the disease, such as hydroxychloroquine (HCQ), statins, and certolizumab pegol (CTZ). As for HCQ, a group of experts recommended HCQ in addition to conventional treatment in those with APS and with previous pregnancy failure on current treatment [88]. Furthermore, an international task force highlighted the need for clinical trials of HCQ in pregnant women with aPL and APS [89]. In vitro studies suggested that HCQ inhibits aPL binding to trophoblasts restoring their function [90]; in a recent mouse model of ob-APS, HCQ at a dose similar to the therapeutic dose in human, prevented fetal death even the ex vivo gamma counting, and immunohistochemical analysis did not affect the aPL binding to the placenta [91•]. Three retrospective studies have showed the benefits of HCQ in improving APOs in APS patients in addition to conventional treatment [92–94]. In a recent multicenter retrospective study, high HCQ (400 mg/day) versus low HCQ (200 mg/day) and its administration before versus during pregnancy was associated with a significantly higher live birth rate in APS patients without previous thrombosis [87•]. The HYPATIA study, a multicenter randomized clinical trial (RCT), will start in the near future. This will evaluate the efficacy of HCQ versus placebo in addition to standard of care in women with persistent aPL planning for pregnancy [95]. The HYDROSAPL, a French RCT, will assess the efficacy of the addition of HCQ to conventional treatment during pregnancy in ob-APS and thrombotic APS [96] (Table 3).

Due to the similarities in pathophysiology among PE, IUGR, and atherosclerotic cardiovascular disease, statins have been proposed for treating and/or preventing these obstetrical complications. Lefkou et al. reported on a small, observational trial that showed a dramatic improvement in both maternal and fetal/neonatal outcomes in women with APS given pravastatin (20 mg/day) in addition to LDA and heparin after the onset of PE and/or IUGR compared with women in the control group on conventional treatment [97•]. The protective effects of pravastatin on the endothelium together with its effect in restoring angiogenic balance might explain the amelioration of placental and maternal preeclamptic signs. Keeping in mind the potential role of TNF in the development of obstetric complications, an ongoing trial, the Improve Pregnancy in APS with Certolizumab Therapy (IMPACT) study is evaluating if CTZ, a TNF inhibitor that does not cross the placenta [98], reduces the risk of APOs in high-risk APS patients [99] (Table 3).

Thrombotic and Obstetric APS

In ob-APS women with a history of a previous thrombotic event, the treatment is based on secondary thromboprophylaxis by using anti-thrombotic drugs and preventive strategies to minimize the risk of recurrent thrombosis and reduce APOs [100]. Since APS women with a previous thrombosis are usually treated with anticoagulation therapy, particularly with vitamin K antagonist (VKA), it is important for these women to discontinue VKA and switch to *therapeutic* LMWH and LDA [101, 102], as soon as pregnancy is confirmed in order to avoid fetal warfarin syndrome [103, 104], as a consequence of the exposure to warfarin between the 6th and 12th gestational week. In some countries (e.g., Brazil), the use of VKA is considered from the 13th week until the 36th week of gestation [105], because of the impracticability of LMWH due to its cost.

Antithrombotic Management During the Delivery Period

Another important aspect is the management of antithrombotic and anti-platelet medications in these women during delivery and the puerperium period. Even though the time to stop treatment remains controversial, this depends mostly on local protocols and the type of delivery programmed by the obstetrician. Discontinuation of LDA depends on the centers anesthesiologist experience and implemented hospital protocol. It is recommended that patients on anticoagulation with

Table 3 Human studies evaluating novel therapies in ob-APS

Drug	Study, year	Type of study	Population (*n*)	Main findings
HCQ	Mekinian A et al., 2015	Observational retrospective	APS [49] with 35 pregnancies	LDA + LMWH vs HCQ + LDA + LMWH: significant decrease of PrL from 81 to 19%
	Sciascia S et al., 2016	Observational retrospective	98 aPL-positive women with 174 pregnancies (51 HCQ + LDA + LMWH vs 119 LDA + LMWH)	HCQ + LDA + LMWH: higher rate of live births and a lower prevalence of overall pregnancy morbidity
	Ye SL et al., 2017	Observational retrospective	APS with RSA (126 $PDN^{0–14w}$ + HCQ + LDA + LMWH; 141 LDA + LMWH)	PDN + HCQ + LDA + LMWH: decrease in the incidence of repeat PrL, miscarriage, and placental dysfunction-related diseases and a significant increase in pregnancies lasting longer than 24 w
	Ruffatti et al., 2018	Observational retrospective	Pregnant APS patients (194)	HCQ 400^{mg} vs 200^{mg}, HCQ before vs during pregnancy: significant increase in the live birth rate
	HYPATIA, ongoing	Double-blind RCT	aPL carriers and APS women who are planning pregnancy (target sample size: 328)	HCQ + LDA-LMWH vs placebo + LDA + LMWH. Endpoint: rate of APOs
	HYDROSAPL ongoing	Double-blind RCT	ob-APS and t-APS during pregnancy (target sample size: 220)	HCQ + LDA-LMWH vs placebo + LDA + LMWH. Endpoint: rate of uncomplicated pregnancy
Pravastatin	Lefkou E et al., 2016	Retrospective	ob-APS with PE and/or IUGR (11 pravastin + LDA + LMWH vs 10 LDA + LMWH)	Pravastatin (20 mg/d) + LDA + LMWH: increased placental blood flow and improvements in PE features
Eculizumab	Gustavsen A et al., 2017	Case report	An APS pregnant woman with previous arterial thrombosis and ongoing leg ischemia	Two dose of eculizumab (600 mg 8 and 1 day) before delivery: ischemic symptoms declined following the 1st dose and no adverse effects were seen.
CTZ	IMPACT, ongoing	Open-label trial	High risk pregnant patients with APS or SLE (target sample size: 50)	CTZ + LDA + LMWH. Endpoint: 1) rate of APOs in women with clinical APS and LAC, and 2) alterations in angiogenic markers of poor placental vascularization

aPL antiphospholipid antibodies, *APOs* adverse pregnancy outcomes, *APS* anti-phospholipid syndrome, *CTZ* certolizumab pegol, *HCQ* hydroxychloroquine, *HYPATIA* HYdroxychloroquine to improve Pregnancy outcome in women with AnTIphospholipid Antibodies, *IMPACT* IMProve pregnancy in APS with Certolizumab Therapy, *IUGR* intrauterine grow restriction, *LDA* low-dose aspirin, *LMWH* low molecular heparin, *PDN* prednisolone, *PE* pre-eclampsia, *PrL* pregnancy losses, *RCT* randomized clinical trial, *RSA* recurrent secondary abortion, *SLE* systemic lupus erythematosus

LMWH (at week 36–37) should switch to UFH and stop 4–6 h prior to elective induction of delivery, cesarean section, or neuraxial anesthesia [85]. However, if the patient is maintained on *prophylactic*/*therapeutic* LMWH, this should be suspended 24 h prior to elective induction of delivery, cesarean section, or neuraxial anesthesia.

Catastrophic APS

A special attention should be given to a rare and life-threatening condition of APS called catastrophic antiphospholipid syndrome (CAPS) that can develop in women during pregnancy [106]. The current management remains challenging and consists as first-line therapy: (1) anticoagulation, (2) pulse of corticosteroids, and/or (3) plasmapheresis, and/or (4) IVIG infusions [106]. In severe cases of CAPS refractory to multiple treatments, current literature reports successful cases using a second-line therapy with rituximab or eculizumab. The latter has been suggested in several recent reports as a second-line treatment option in APS and CAPS [106, 107], and recent data has shown that only trace amounts of eculizumab passes the placenta [108•].

Associated Autoimmune Diseases in aPL/APS Women

The treatment of patients with ob-APS associated to other autoimmune diseases should include HCQ in association to LDA and *prophylactic* or *therapeutic* heparin depending on the clinical (with or without previous thrombosis) and laboratory (low- vs high-risk) profile [80••]. It is still unknown the risk of obstetric complications in aPL carriers, women positive for aPL but without obstetric and thrombotic manifestations of APS, or in women with obstetric morbidity not fulfilling criteria for APS. Considering the pathogenic role of the aPL, a stratification risk should be taken into account based on the same risk factors mentioned above for definite ob-APS.

To date, few studies have been investigated the risk of APOs in these women making it difficult to draw

conclusions given the heterogeneity of type and number of aPL tested [59•, 109–111]. LDA, also used in women without aPL for the prevention of PE [112], has not been shown to have efficacy as primary prophylaxis in reducing APOs in aPL carriers; but this systematic review included only five studies involving 154 pregnancies [113]. However, in clinical practice, LDA is generally used to manage aPL carriers during pregnancy, especially if one or two fetal losses or maternal risk factors are present [114]. In a large retrospective observational study, the rate of pregnancy losses, gestational weight at delivery, and birth weight percentile was not different between aPL positive women treated with LDA and those not treated [109]. The same data was confirmed in another large cohort of 73 pregnant aPL carriers (mostly isolated LA) [110]. More recently, in a multicenter study, among 200 pregnant women positive for aPL, aPL carriers experienced a similar number of APOs compared to ob-APS (18%) and thrombotic APS (24%); triple aPL positivity was associated to APOs even in aPL carriers on treatment with LDA plus LMWH [60]. In another multicenter study [111], APOs were observed in 9% of aPL carriers and were associated to acquired traditional risk factors, "APS non-criteria" or "lupus-like" manifestations and triple aPL positivity. Interestingly, APOs occurred despite combination treatment with LDA and *prophylactic* LMWH, suggesting that aPL carriers with multiple risk factors and a "high-risk" aPL profile may require additional treatment, such as *therapeutic* LMWH or HCQ. In the first-year analysis of the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS), women with obstetric morbidity not fulfilling criteria for APS had APOs similar to those with ob-APS and benefit from the combination therapy with LDA and *prophylactic* LMWH [78]. The beneficial role of HCQ in pregnant aPL carriers has been hypothesized [115, 116], and the RCT HYPATIA will assess the role HCQ in reducing APOs in aPL carriers, too [95].

Perspectives

Promising results have been observed for novel pharmacological mechanisms that could prevent the binding of either β2GPI or aβ2GPI to the trophoblast surface: the binding site of domain V of β2GPI can be targeted by the synthetic peptide TIFI [117]; a non-complement fixing antibody to β2GPI domain 1 can prevent the binding between aPL and β2GPI [118]; the ob-APS phenotype can be attenuated by the induction of tolerogenic dendritic cells specific for β2GPI domain 1 [119]; and the binding site of β2GPI to its receptors can be inhibited by the 1N11 monoclonal antibody [120].

Conclusions

Besides thrombotic microangiopathy, new pathogenic pathways involving uncontrolled inflammation support the development of poor pregnancy outcomes. Further studies are required to deepen our understanding of how aPL cause ob-APS and to clarify the epidemiology of ob-APS and its different subsets. The current treatment regimen to prevent obstetric morbidity in APS is based on LDA and heparin; this approach has improved pregnancy outcomes to a live birth rate of over 70%. As nearly 30% of women continue to have pregnancy complications, further studies are ongoing to assess different options in order to improve pregnancy outcomes in women with APS, especially in refractory ob-APS and aPL carriers. HCQ seems to be a promising drug, based on experimental and clinical studies. Other drugs interacting with the pathogenic mechanisms of ob-APS such as eculizumab and statins could be considered in selected complex cases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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